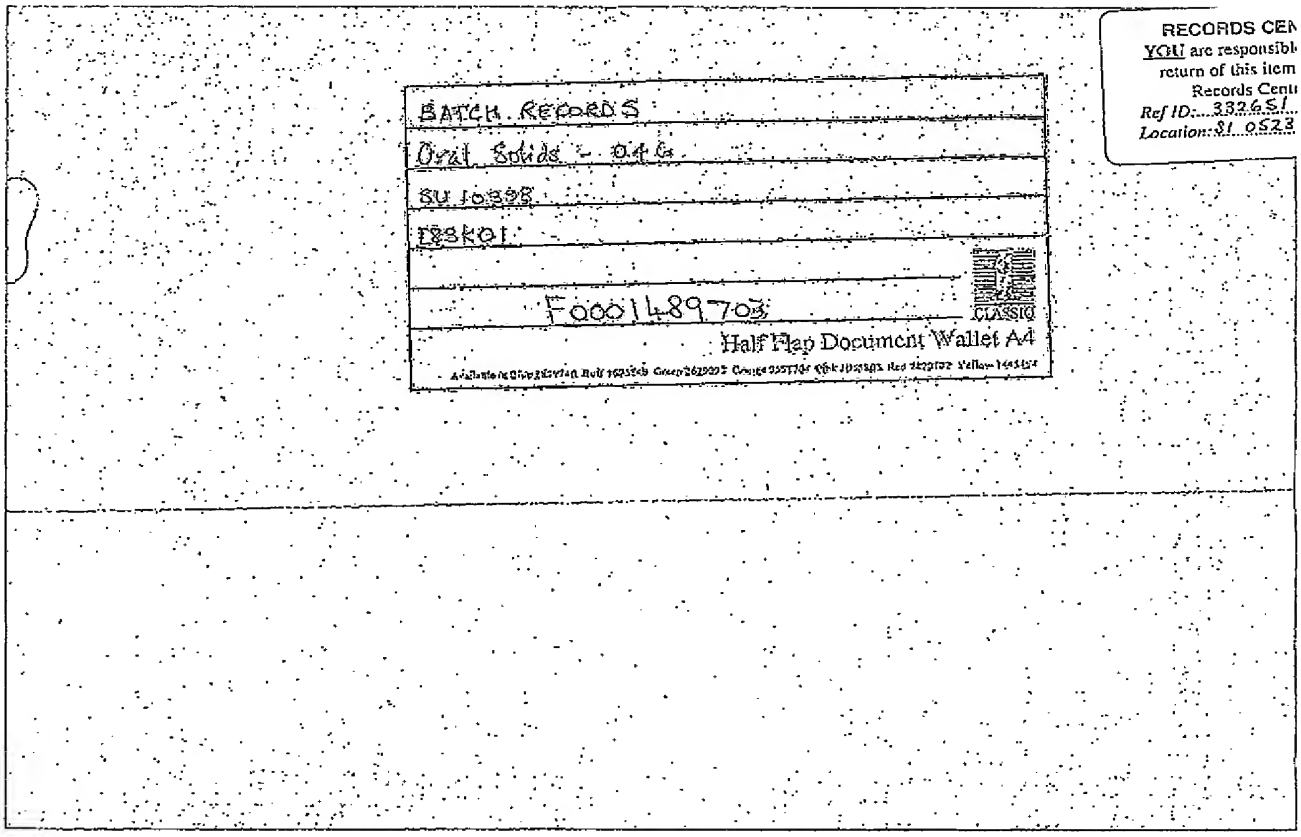
ANNEX 1

F0001489703 - I83K01



Pharmacia & Upjohn

Pharmaceutical Development / *Oral solids and warehousing*

# PROCESSING SHEET

PAGE: 1 of *20*

PRODUCT: SU10398 LOT: I83K01

PHARMACEUTICAL FORM: Granulated DOSAGE: 75% W/W in API COMM.: *RD0511P0SUG*

FORMULA No.: PREPARATION DATE: *04 / 01*

PROCESSING START: *10 / 04 / 02* PROCESSING FINISH: *11 / 04 / 01*

THEORETICAL QUANTITY: *46663* (T) QUANTITY OBTAINED: *4280* yield: *91.7* %

SCOPE OF THE PREPARATION: Stability studies and clinical trial

## THEORETICAL UNITARY FORMULA

| RAW MATERIAL | | SPECIFICATIONS | M.U. | UNIT DOSE *SEE NOTE | Over Dose |
|---|---|---|---|---|---|
| *SU10398* | Active principle | | *mg* | *75.0* ** *NOTE 2* | |
| *MANNITOL* | Excipient compensation | | *mg* | *13.5* | |
| *CROSCARMELLOSE SODIUM* | | | *mg* | *3.0* | |
| *POLYVINYLPYRROLIDONE K25* | | | *mg* | *5.0* | |
| * ~~COMPLETION~~ * | | | | | |
| *CROSCARMELLOSE SODIUM* | | | *mg* | *3.0* | |
| *VEGETABLE MAGNESIUM STEARATE* | | | *mg* | *0.5* | |
| *TOTAL* | | | *mg* | *100.0* | |
| *NOTE: THE UNIT DOSE IS EXPRESSED IN RESPECT TO 100 mg TOTAL OF GRANULATE | | | | | |
| [initials] *06.04.01* | [initials] *06/04/01)* | | | | |
| **NOTE: 75 mg EXPRESSED AS MALATE SALT ~~(EQUIVALENT TO 65 mg FREE BASE)~~ [initials] *06/04/01* | | | | | |
| | [initials] *06/04/01* | | | | |

Signature of who filled out the form:

[signature]

Approval for use by the Chief of ORAL SOLIDS and WAREHOUSING:

[signature]

Edition No.: 7 of 10/05/99
Substitutes Edition No.: 6 of 03/11/97

Product: SU10398 Lot: I83K01 Page: 2 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

## PRACTICAL FORMULATION

| RAW MATERIALS | CODE | LOT No. | TITER | Over dose | M.U. | PRACTICAL UNIT DOSE | M.U. | Practical quantity per 4666.3 g |
|---|---|---|---|---|---|---|---|---|
| *1) GRANULATE* | | | | | | | | |
| *SU10398* | *1502* | * NOTE 97.93% | | | *mg* | *76.585* | *g* | *3574.0* |
| *MANNITOL* | *723* | *AE130* | | | *mg* | *11.915* | *g* | *556.0* |
| *CROSCARMELLOSE SODIUM* | *920755200* | *AA10E113* | | | *mg* | *3.000* | *g* | *140.0* |
| *POLYVINYLPYRROLIDONE K25* | *931563000* | *AA10G041* | | | *mg* | *5.000* | *g* | *233.3* |
| *2) COMPLETION* | | | | | | | | |
| *CROSCARMELLOSE SODIUM* | *920755200* | *AA10E113* | | | *mg* | *3.000* | *g* | *140.0* |
| *VEGETABLE MAGNESIUM STEARATE* | *927406000* | *AA10L028* | | | *mg* | *0.500* | *g* | *23.3* |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | [initials] *06/04/01* | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| *Verified the practical titer calculation and approved* – [signature] *06.04.01* | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

[initials] *06.04.01*

**NOTE:** *THE ANALYTIC TITER OF THE API IS EXPRESSED IN RESPECT TO THE FREE BASE AND IS 73.3%. THE THEORETICAL TITER WITH RESPECT TO THE FREE BASE IS : 50/66.3 x 100 = 74.85%, OF WHICH A PRACTICAL TITER OF 97.93% IS OBTAINED AS EXPRESSED ON THE API AND USED FOR THE PRACTICAL DOSE*

Operator's signature: [signature]

Verifier's signature: [signature]

Edition No.: 7 of 10/05/99
Substitutes edition No.: 6 of 03/11/97

Checked by: [signature]

* *NOTE 2: UNIT DOSE EXPRESSED PER 100 mg OF GRANULATE*

| | | |
|---|---|---|
| Product: SU10398 | Lot: I83K01 | Page: *3* of *20* |
| Pharmaceutical form: Granulated | Dosage: 75% W/W in API | |

## ACTIVE PRINCIPLE: VERIFICATION OF THE PRACTICAL QUANTITY CALCULATIONS AND AVERAGE TITER

Active principle: *SU 10398* Provided quantity: _____ A)
Lot: *(A) – 5975-HTM-0002-N2* Titer as sampled: _____

Active principle: _____ Provided quantity: _____ B)
Lot: _____ Titer as sampled: _____

Active principle: _____ Provided quantity: _____ C)
Lot: _____ Titer as sampled: _____

| | | | | |
|---|---|---|---|---|
| Total theoretical quantity | (Pt) | = | _____ g | (Unit dose x theoretical launch quantity) |
| Calculated theoretical quantity | (Pc) | = | _____ g | (A x Tit. A ÷ B x Tit. B ÷ C x Tit. C) |
| Total practical quantity | (Pp) | = | _____ g | (A ÷ B + C) |

**NOTE:**
1) The correspondence between the weighed active principle quantity and the practical active principle to be used is verified when **Pt = Pc.**
This correspondence is also verified when the two values differ and the divergence between the provided quantity and the requested quantity is due exclusively to the weighted values in accordance with the divergence limits set out in procedure SF.TF 015/0 **(±0.5%)**.
2) If the condition in point 1) is not fulfilled, suspend the processing and inform the Lot Formation Center.
3) If the condition in point 1) is fulfilled, proceed to fill in the following points on this page.

*NOT NECESSARY SINCE THE API WILL BE WEIGHED IN THE DEPARTMENT* [initials] *06 APRIL 2001*

Average titer weight = Pt/Pp x 100 = ..... %

Active principle: .....

Quantity to use = Pt/Titer* x 100 = ..... g (D)

Compensation excipient: .....

Quantity to use = Pe – (D – Pt) = ..... g

**NOTE:**
Pt = Weight in grams of the active principle considering a 100% titer
Pe = Compensation excipients weight in function of the active principle at 100% titer
* = Should multiple lots be used, the titer will be the average weight, as calculated considering the quantity of each lot.

**Operator's signature:** _____ **Verifier's signature:** _____

| | | |
|---|---|---|
| Product: SU10398 | Lot: I83K01 | Page: *4* of *20* |
| Pharmaceutical form: Granulated | Dosage: 75% W/W in API | |

## CLEANING OF THE EQUIPMENT AND ROOMS

Once the processing has been completed clean the processing rooms with: *5% PYRONEG AQUEOUS SOLUTION*

*(CLEANING METHOD SO/OM/019)*

Once the processing has been completed, clean the equipment with: *5% PYRONEG AQUEOUS SOLUTION*

*(CLEANING METHOD SO/OM/019)*

## PROCESSING IDENTIFICATION LABELS

| | | | | | | |
|---|---|---|---|---|---|---|
| CONFORMITY VERIFICATION LABELS | | | DATE: | *06/04/01* | SIGNATURE: | [signature] |
| LABELS DELIVERED | No.: *32* ~~*10/04/01*~~ | | DATE: | *10/04/01* | SIGNATURE: | [signature] |
| ADDITIONAL DELIVERED | No.: | | DATE: | | SIGNATURE: | |
| LABELS USED | No.: ~~*20*~~ *22* | | DATE: | *11/04/01* | SIGNATURE: | [signature] |
| DETERIORATED LABELS | No.: | | DATE: | | SIGNATURE: | |
| LABELS RETURNED | No.: [initials] *21/5/01* *10* | | DATE: | *11/04/01* | SIGNATURE: | [signature] |

(The returned labels are destroyed)

## LABEL MODEL

**Pharmacia & Upjohn** – *Oral Solids Section*

Granulated SU10398 75% W/W in API

LOT: I83K01 Prep. Date: 04/2001

FORMULA No.:

.....

Date: *10/04/01* Label No. 16 of 16

[initials] *06/04/01*

NOTE: _____

**Pharmacia & Upjohn** – *Oral Solids Section*
Product: Granulated SU10398 75% W/W in API
LOT: I83K01
FORMULA No.:
Prep. Date: 04/2001
Date: *10/04/01* .....
[signature] Label No. 16 of 16

Pharmacia & Upjohn

Pharmaceutical Development / *Oral solids and warehousing*

Product: SU10398 Lot: I83K01 Page: 5 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API Room: 72

**WEIGHT VERIFICATION OF THE RAW MATERIALS**

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| *01 004 10* | 1 | [initials] *06/04/01*<br>~~Check the weight of the active principle/s~~<br>*ACCORDING TO THE INDICATIONS IN THE SCHEDULED DEVIATION PROCEDURE NUM. 13/01 WEIGH OUT THE INDICATED QUANTITY OF THE ACTIVE PRINCIPLE.* | | [signature] | [signature] |
| | 1/1 | PRODUCT: [initials] *06/04/01*<br>[initials] *06/04/01*<br>~~*SU 10248*~~ *SU10398*<br>LOT: *(A) 5975-MTM-0002-N2*<br>PRACTICAL WEIGHT *3574.0* g | Lot: *(A)5975-MTM-0002-N2*<br>Gross: *3874* g<br>Tare: *300* g<br>Net: *3574* g<br>Scale ID No.: *50-BC-32* | | |
| | 1/2 | PRODUCT:<br>LOT:<br>PRACTICAL WEIGHT g | Lot:<br>Gross: g<br>Tare: g<br>Net: g<br>Scale ID No.: | | |
| | | [initials] *02/05/01* | | | |
| | 1/3 | PRODUCT:<br>LOT:<br>PRACTICAL WEIGHT g | Lot:<br>Gross: g<br>Tare: g<br>Net: g<br>Scale ID No.: | | |

**Edition No.: 7 of 10/05/99**
**Substitutes edition No.: 6 of 03/11/97**

**Checked by:** [signature]

Product: SU10398 Lot: I83K01 Page: *6* of *20*

Pharmaceutical form: Granulated Dosage: 75% W/W in API Room: *72*

**WEIGHT VERIFICATION OF THE RAW MATERIALS**

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 2 | **Check the weight of the following raw materials:** | | | |
| *10/ 04/ 01* | 2/1 | PRODUCT: *MANNITOL*<br>LOT: *AE130*<br>PRACTICAL WEIGHT *556.0* g | Lot: *AE130*<br>Gross: *569.00* g<br>Tare: *13.00* g<br>Net: *556.00* g<br>Scale ID No.: *SO/BL/32* | [signature] | [signature] |
| | 2/2 | PRODUCT: *CROSCARMELLOSE SODIUM S10*<br>LOT: *AA10E113*<br>PRACTICAL WEIGHT *140.0* g | Lot: *AA10E113*<br>Gross: *153.00* g<br>Tare: *13.00* g<br>Net: *140.00* g<br>Scale ID No.: *SO/BL/32* | [signature] | [signature] |
| *10/ 04/ 01* | 2/3 | PRODUCT: *POLYVINYLPYRROLIDONE K25*<br>LOT: *AA10G041*<br>PRACTICAL WEIGHT *233.3* g | Lot: *AA10G041*<br>Gross: *246.30* g<br>Tare: *13.00* g<br>Net: *233.30* g<br>Scale ID No.: *SO/BL/32* | [signature] | [signature] |
| | 2/4 | PRODUCT:<br>LOT:<br>PRACTICAL WEIGHT g | Lot:<br>Gross: g<br>Tare: g<br>Net: g<br>Scale ID No.: | | |
| | 2/5 | [initials] *02/05/01*<br>PRODUCT:<br>LOT:<br>PRACTICAL WEIGHT g | Lot:<br>Gross: g<br>Tare: g<br>Net: g<br>Scale ID No.: | | |

**Edition No.: 7 of 10/05/99**
**Substitutes edition No.: 6 of 03/11/97**

**Checked by:** [signature]

Pharmacia & Upjohn

# Pilot Plan Formula Development

*Oral Solids Section*

Product: SU10398 Lot: I83K01 Room: 72 Page: 7 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

WET GRANULATION in DIOSNA

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 3 | **Preparation of the granulated solution** | | [signature] | [signature] |
| 01/04/10 | 3/1 | Using a sterile container, collect approximately 150 mL of contrast T.D.I. Water to be used and send the sample to determine its bacterial load. | T.D.I. Water Contrast No.: 42<br>mL collected: 300 | | |
| | 3/2 | Weigh out 610 g of TDI WATER<br>SEE NOTE [initials] 06/04/01<br>Warm the solvent to a temperature between ....°C and ....°C and disperse under shaking:<br>Let it cool until a practically clear solution is obtained.<br>[initials] 06/04/01<br>Addition of tensioactive agents ☐<br>Weight ....g of ....<br>Warm the solvent to a temperature between ....°C and ....°C and disperse under shaking:<br>Combine the tensioactive solution with the solution of point .... under shaking. | Solvent Quantity<br>Gross: 753 g<br>Tare: 143 g<br>Net: ~~610+600~~ g 10/04/01 [initials]<br>Temperature: ~~TOTAL $H_2O$ 1210 mL~~ °C<br>*Room temperature*<br>☐<br>Solvent Quantity per Tensioactive<br>Gross: ....g<br>Tare: ....g<br>Net: ....g<br>Temperature: ....°C<br>☐ | [signature] | [signature] |

Edition No.: 7 of 10/05/99
Substitutes edition No.: 6 of 03/11/97

Checked by: [signature]

Pharmacia & Upjohn

# Pilot Plan Formula Development

*Oral Solids Section*

Product: SU10398 Lot: I83K01 Room: 72 Page: 8 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

WET GRANULATION in DIOSNA

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| 01 04 10 | 4 | **Preliminary sieve analysis of the raw materials** | | [signature] | [signature] |
| | 4/1 | Sieve analyze the raw materials<br>*MANNITOL*<br>*CROSCARMELLOSE SODIUM*<br>*POLYVINYLPYRROLIDONE K25*<br><br><br>through a *1-1,5 mm*<br>gauge sieve | Equipment used:<br>*SIEVE*<br>ID number: *1*<br>Cleaning verification: *OK*<br>Gauge: *1 mm* | | |
| | 4/2 | Equipment type:<br>*SIEVE* | | | |
| 01 04 10 | 5 | **Mixing**<br>*OF POINTS*<br>Load the raw materials from point *1 2 2*<br>into the Diosna granulator and mix for *4*<br>minutes under the following conditions:<br>Principle shaker speed: *I*<br>Crusher speed: *I*<br>**MODIFY IN PROCESS IF NEEDED*<br>[initials] *06/04/01* | ID number:: *SO.9U.DA*<br>Cleaning verification: *OK*<br><br>Principle shaker speed: *I*<br>Crusher speed: *I*<br>Start time: *14:03* End time: *14:07* | [signature] | [signature] |
| 01 04 10 | 6<br>6/1 | **Wetting**<br>Wet the powder with the solution prepared<br>in point 3/2<br>Using a peristaltic pump ☒<br>* *MODIFY THE FOLLOWING PROCESS IF NEEDED* [initials] *06/04/01*<br>Pump capacity *250-350* g/min.<br>During the wetting employ the following conditions:<br>Principle shaker speed: *I*<br>Crusher speed: *I* | Peristaltic pump model:<br>*LOHER*<br>ID number *SO-PM-07*<br>Cleaning verification: *OK*<br>Pump capacity *280* g/min.<br>Pump r.p.m. *38-40*<br>Principle shaker speed: *I*<br>Crusher speed: *I*<br>Start time: *14:10* End time: *14:15* | [signature] | [signature] |

Product: SU10398 Lot: I83K01 Room: 72 Page: 9 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

WET GRANULATION in DIOSNA

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| 01 04 10 | 6/2 | *IN ACCORDANCE WITH THE FINAL NOTE,* [initials] *06/04/01* ~~If needed~~, add *THE APPROPRIATE QUANTITY OF WATER* at the end of the wetting while keeping the conditions from point *6/1* unchanged. *RECORD THE QUANTITY OF ADDED WATER IN EACH SINGLE PART.* *STOP ADDING WATER WHEN THE MIX IS JUDGED TO BE SUFFICIENTLY WET.* [initials] *06/04/01* | Solvent type: *T.D.I $H_2O$* Added quantity: *600* T.D.I. Water contrast No.: *42* Start time: ..... End time: ..... *DATA NOT REGISTERED IN PROCESS* *02/05/02* | [signature] | [signature] |
| | 6/3 | If the T.D.I. Water contrast is different from that in point *3*, using a sterile container, collect approximately *150* ml of T.D.I. Water and send the sample to have its bacteria load determined. | T.D.I. Water contrast No.: ..... mL collected: ~~.....~~ [initials] *02/05/01* | | |
| 01 04 10 | 7 | **Granulation** | | [signature] | [signature] |
| | 7/1 | Proceed to the granulation of the wet mass according to the following parameters: Principle shaker speed: *I/II* Crusher speed: *I/II* * Granulation time: *At least 1* | Principle shaker speed: *I I'30"* Crusher speed: *I I'30"* Principle motor electricity absorption at the end of granulation: *58* A *2.90* Granulation time: *3 '* | | |
| | | ** CHOOSE AND ADAPT THE CONDITIONS AND TIME BASED ON THE BEHAVIOR OF THE MIX IN GRANULATION.* [initials] *06/04/01* | *II I'30"* *II I'30"* | | |

Edition No.: 6 of 03/11/97
Substitutes edition No.: 5 of 15/09/97

Checked by: [signature]

Product: SU10398 | Lot: I83K01 | Room: 72 | Page: 10 of 20

Pharmaceutical form: Granulated | Dosage: 75% W/W in API | WET GRANULATION in DIOSNA

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 8 | **Drying** | | | |
| 01<br>04<br>10 | 8/1 | Transfer the wet granulated mass into the *GLATT GPCG 5* type dryer and dry at a relative humidity of ≤ *2.5* % according to the following parameters:<br>**Heater** ☐<br>[initials] *06/04/01*<br>Temperature: ..... °C<br>In a vacuum at ..... ☐<br>At an atmospheric pressure of ☐<br>**Fluid bed dryer** ☐ | Equipment: .....<br>*GLATT GPLG 5*<br>ID number: *SO-LF-02*<br>Cleaning verification: *OK*<br>[initials] *06/04/01*<br>Temperature read: ..... °C<br>Degree of vacuum: .....<br>Start time: ..... End time: ..... | [signature] | [signature] |
| | 9 | | | | |
| | 9/1 | "AIR IN" Temperature: *60* °C<br>"AIR IN" Volume: *120-160* $Nm^3/h$ | "AIR IN" Temperature: *60* °C<br>"AIR IN" Volume: *120* $Nm^3/h$ | | |
| | 9/2 | Product temperature to set on the thermometric probe: *40* °C | Temperature set on the probe: *10* °C | [signature] | [signature] |
| | 9/3 | Time for shaking the hoses: *15"* | Time for shaking the hoses: *10"* | | |
| | 9/4 | Time between hose shakings: *3* minutes | Time between hose shakings: *2* minutes | | |
| | 9/5 | Shaking Type WSG ☐ GPCG ☒ | Shaking Type WSG ☐ GPCG ☒<br>Start time: *15:20*<br>End time: *16:00* | | |
| | | | "AIR OUT" Temperature at the end of the process: *38*°C | [signature] | [signature] |

Edition No.: 6 of 03/11/97
Substitutes edition No.: 5 of 15/09/97

Checked by: [signature]

Product: SU10398 | Lot: I83K01 | Room: 72 | Page: 11 of 20

Pharmaceutical form: Granulated | Dosage: 75% W/W in API | WET GRANULATION in DIOSNA

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 9/6 | At the end of drying, sample the granulated mass from the dryer according to the manner described in SOP SG.CF 004 and perform the following checks: | | | |
| 01 04- 11- | - | Karl Fisher: ☐ | Residual humidity: : 1.03 % | [signature] | [signature] |
| | 9/7 | Weight loss at 110 °C ~~for~~ UNIT A CONSTANT WEIGHT | Thermobalance at 110 °C for 20 min | | |
| | 9/8 | IS REACHED ~~min.~~ [initials] 06/04/01 ☒ | Thermobalance ID number: SO-BL-42 | | |
| | | Residual humidity limit ≤2.5 % | Karl Fischer ID number: ..... [initials] 06/04/01 | | |
| | 9/9 | If the residual humidity value is not within the set limits, continue drying according to the provisions in point 9/1 | ☐ | | |
| | - | If necessary modify: | | | |
| | | -the drying temperature ☐ | "AIR IN" Temperature: ..... °C<br>Heater temperature: ..... °C | | |
| | 9/10 | -the thermometric probe product temperature ☒ | Thermometric probe product temperature: ..... °C<br>Start time: ..... End time: .....<br>"AIR OUT" temperature at the end of the process: ..... °C | | |
| | 9/11 | At the end of drying, sample the granulated mass from the dryer according to the manner described in SOP SG.CF 004 and perform the following checks again: | [initials] 02/05/01 | | |
| | | Karl Fisher: ☐ | Residual humidity: :..... % | | |
| | 9/12 | Weight loss at 110 °C ~~for~~ UNIT A CONSTANT WEIGHT | Thermobalance at ..... °C for ..... min | | |
| | | IS REACHED ~~min.~~ [initials] 06/04/01 ☒ | Thermobalance ID number: ..... | | |
| | 9/13 | Residual humidity limit ≤2.5 % | Karl Fischer ID number: ..... | | |

Product: SU10398 Lot: I83K01 Room: 72 Page: 12 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

**WET GRANULATION in DIOSNA**

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 10 | **Final Calibration** | | | |
| 01<br>04<br>10 | 10/1 | Calibrate the dried granulated mass using *VIANI OSCILLATING GRANULATOR* | Equipment used: *VIANI OSCILLATING GRANULATOR* | [signature] | [signature] |
| | 10/2 | that is equipped with a sieve with a gauge of *1000* µm | ID number: *SO-GS-03*<br>Cleaning verification: *OK*<br>Gauge: *1000* µm<br>Start time: *16:10* End time: *16:15* | | |
| | 10/3 | At the end of calibration, collect the granulated mass obtained in the appropriate container/s of *DOUBLE P.E. BAG* | ☒ | | |

Product: SU10398 Lot: I83K01 Room: 72/69 Page: 13 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

Granulation completion

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| 11.04.01 | 11 | **Technological controls** | | [signature] | [signature] |
| | 11/1 | Sample 50 g of granulate according to SOP SF.CF 004 and carry out the following controls: | Quantity sampled: 50 g | | |
| | | Apparent density (SOP SF.TF 036) ☒ | Equipment: ..... | | |
| | 11/2 | Limit of: N.A. g/mL | Quantity of mix used: 50 g<br>$V_0$: 92 mL *HOLES APPEAR AND DATA NOT RECORDED IN PROCESS* [initials] *02/05/01*<br>$V_{10}$: ..... mL $V_{500}$: ..... mL<br>$V_{1250}$: ..... mL $V_{2500}$: ..... mL<br>Da = 82 / α543 g/mL Di = ..... g/mL<br>*14/04/01* [initials] | | |
| | | Granulometry (SOP SF.TF 034) ☒ | Equipment: *JEL 200 SO/SU/01* | | |
| | 11/3 | Limits | Quantity of mix used: 50 g | | |
| | | > 1000 µm: 2.1 % | > 1000 µm: 0 % | | |
| | | between 710 and 1000 µm: N.A. % | between 710 and 1000 µm: ~~1~~ ~~0.50~~ 1.00 % | | |
| | | between 500 and 710 µm: N.A. % | between 500 and 710 µm: 5.04 ~~2.52~~ 504 % | | |
| | | between 250 and 500 µm: N.A. % | between 250 and 500 µm: 16.3 ~~8.15~~ 16.30 % | | |
| | | between 106 and 250 µm: N.A. % | between 106 and 250 µm: 20 35.00 % | | |
| | | < 106 µm: N.A. % | < 106 µm: 66 3.83 % | | |
| | 1- | **Analytic controls** [initials] | *06/04/01* | | |
| | | Collect ..... (number of) granulated samples (in duplicate), according to SOP SF.CF-004 and send them to analysis for homogeneity control. | Quantity sampled: ..... g<br>See analytical controls in process | | |
| 11.04.01 | 12 | **Granulation yield control** | **Granulation obtained:** | [signature] | [signature] |
| | 12/1 | Determine the net quantity of granulated mass obtained from the sampling for technological and analytical controls. | Gross: 4460 g<br>Tare: 300 g<br>Net: 4160 g (D) | | |
| | 12/2 | Granulation yield % = D / theoretical<br>*Theoretical 4503.3g* | GRANULATION YIELD % = 92.38 (E) | | |

Product: SU10398 Lot: I83K01 Room: 72 Page: 14 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

**Granulation completion**

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| 10. 04. 01 | 13<br>13/1 | **Mix preparation**<br>Redo the proportions and weigh the excipients listed below based on the granulation yield (**E**) calculated in point 12/2 Send the residual excipients to be destroyed. | ☐ | [signature] | [signature] |
| | 13/2 | CROSCARMELLOSE SODIUM<br>Quantity to be weighed = 140.0 g x E/100 = 129.3 g<br>Lot: AA10E113 | Lot: AA10E113<br>Gross: 135.30 g<br>Tare: 6.00 g<br>Net: 129.30 g<br>Scale ID number: SO-BL-32 | | |
| | | VEGETABLE MAGNESIUM STEARATE<br>Quantity to be weighed = 23.3 g x E/100 = 21.52 g<br>Lot: AA10L028 | Lot: AA10L028<br>Gross: 27.52 g<br>Tare: 6.00 g<br>Net: 21.52 g<br>Scale ID number: SO-BL-32 | | |
| | 13/3 | Quantity to be weighed = ..... g x E/100 =<br>Lot: | Lot: .....<br>Gross: ..... g<br>Tare: ..... g<br>Net: ..... g<br>Scale ID number: ..... | | |
| | | Quantity to be weighed = ..... g x E/100 =<br>Lot: | Lot: .....<br>Gross: ..... g<br>Tare: ..... g<br>Net: ..... g<br>Scale ID number: ..... | | |
| | | [initials] 02/05/01<br>Quantity to be weighed = ..... g x E/100 =<br>Lot: | Lot: .....<br>Gross: ..... g<br>Tare: ..... g<br>Net: ..... g<br>Scale ID number: ..... | | |

Product: SU10398 Lot: I83K01 Room: 72 Page: 15 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

Granulation completion

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| 01 04 11 | 14 | **Preliminary sieve analysis of the raw materials** | | [signature] | [signature] |
| | 14/1 | Sieve analyze the raw materials: *CROSCARMELLOSE SODIUM* through a *1-1.5 mm* gauge sieve. Equipment type: *SIEVE* | Equipment used: *SIEVE* ID number: *1* Cleaning verification: *OK* Gauge: *1 mm* | | |
| 01 04 11 | | **Mixing** Load the granulate from point *12/1* and the raw materials that fulfill the provisions of point *13* , with the exception of *VEGETABLE MAGNESIUM STEARATE*, into the *20 LITER 'V' PELLEGRINI* type mixer and mix for *5* minutes at a speed of *35* rpm. | Equipment used: *PELLEGRINI MIXER* ID number: *209 'V' SO-MS-27* Cleaning verification: *OK* r.p.m.: *35* Start time: *14:15* End time: *14:20* | [signature] | [signature] |
| | | Add to the premix described in point *15/1* the *VEGETABLE MAGNESIUM STEARATE* and mix for *5* minutes at a speed of *35* rpm. | Start time: *14:25* End time: *14:30* r.p.m.: *35* | | |
| | | At the end of mixing, empty the mix into the appropriate container of *DOUBLE P.E. BAG* | ☒ | | |

Product: SU10398 Lot: I83K01 Room: 69/72 Page: 16 of 20

Pharmaceutical form: Granulated Dosage: 75% W/W in API

Granulation completion

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | 16 | **Technological controls** | | | |
| 01 04 11 | 16/4 | Sample 50 g of mix according to SOP SF.CF 004 and carry out the following controls: | Quantity sampled: 50 g | | |
| | 16/2 | Apparent density (SOP SF.TF 036) ☒<br>Limit of: N.A. g/mL | Equipment: STAV 2003 (SO/PV/01)<br>Quantity of mix used: 50 g<br>$V_0$: 90 mL<br>$V_{10}$: 76 mL $V_{500}$: 70 mL<br>$V_{1250}$: 70 mL $V_{2500}$: mL<br>Da = 90 / 0.556 g/mL Di = 0.714 g/mL<br>11/04/01 [initials] | [signature] | [signature] |
| | - | Granulometry (SOP SF.TF 034) ☐<br>Limits<br>> 1000 µm: ..... %<br>between 710 and 1000 µm: ..... %<br>between 500 and 710 µm: ..... %<br>between 250 and 500 µm: ..... %<br>between 106 and 250 µm: ..... %<br>< 106 µm: ..... % | Equipment: .....<br>Quantity of mix used: ..... g<br>[initials] 06/04/01<br>> 1000 µm: ..... %<br>between 710 and 1000 µm: ..... %<br>between 500 and 710 µm: ..... %<br>between 250 and 500 µm: ..... %<br>between 106 and 250 µm: ..... %<br>< 106 µm: ..... % | | |
| | - | **Analytic controls** | | | |
| | - | Collect ..... (number of) mix samples (in duplicate), according to SOP SF.CF 004 and send them to analysis for homogeneity control: | [initials] 06/04/01<br>Quantity sampled: ..... g<br>See analytical controls in process | | |
| | 17 | **Final mix yield control** | **Mix obtained:** | | |
| 01 04 11 | 17/1 | Determine the net quantity of mix obtained from the sampling for technological and analytical controls. | Gross: 4610.57 g<br>Tare: 300.25 g<br>Net: 4310.32 g | [signature] | [signature] |



Checked by: [signature]

| Product: SU10398 | Lot: I83K01 | Page: *17* of *20* |
|---|---|---|
| Pharmaceutical form: Granulated | Dosage: 75% W/W in API | |

## IN PROCESS ANALYTICAL CONTROLS

| OPER. No. | DATE | SAMPLE No. | Numeric or ponderal quantity | CONTROL TYPE | LABORATORY | RESPONSE No. and DATE | OPERATOR | VERIFIER |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | [initials] *06/04/01* | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

## TO SEND TO FINISHED PRODUCT ANALYSIS

| DATE | Numeric or ponderal quantity | CONTROL TYPE | LABORATORY | RESPONSE No. and DATE | OPERATOR | VERIFIER |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Product: SU10398 Lot: I83K01 Page: *18* of *20*

Pharmaceutical form: Granulated Dosage: 75% W/W in API

| DATE | OPER. No. | OPERATION DESCRIPTION | PRODUCTION DATA | OPERATOR | VERIFIER |
|---|---|---|---|---|---|
| | | If the results of the sampling sorting are outside the set limits, proceed to unit sorting of the lot as described in the attached form.<br><br>At the end of the sorting operation, send the discarded product to be destroyed. | ☐ [initials] *06/04/01*<br><br>☐ | | |
| *11 04 01* | *18*<br><br>*18/1* | **Counter sampling**<br><br>Sample *1 g OF MIX AND* ~~(number) units and~~ [initials] *06/04/01*<br>package them in: *V.G. BOTTLE* | Quantity sampled: No. *1 g*<br>☒ | [signature] | [signature] |
| *11 04 01* | *19*<br><br>*19/1*<br><br><br>*19/2* | **Final lot yield control**<br><br>Proceed to the quantitative verification of the available product.<br>[initials] *06/04/01*<br>Numeric yield = U / average weight(*)<br>(*) Taken from the final controls<br><br>% Yield = (V / THEORETICAL(*)) * 100<br>(*) T of page 1 | Available product<br>Gross: *4610.31* g *7.08 Gross*<br>Tare: *300.00* g *2800 Tare*<br>Net: *4310.31* g (U) *4280 Net*<br><br>Numeric yield = *~~4310.31~~* [initials] (V)<br>*4280 YIELD No.*<br>[initials] *11/04/01*<br><br>% Yield: *92.37* [initials] (Z)<br>*91.72* | [signature] | [signature] |
| *11 04 01* | *20*<br><br>*20/1* | **Deposit in the warehouse**<br><br>Load the finished product and the counter sample into the SF/Warehouse, stocking them at: *room temperature.* | ☒ | [signature] | [signature] |

Product: SU10398 Lot: I83K01 Page: *19* of *20*

Pharmaceutical form: Granulated Dosage: 75% W/W in API

| DATE | OPERATION No. | NOTES | OPERATOR | VERIFIER |
|---|---|---|---|---|
| *06/04/01* | *3/2, 6/1 and 6/2* | *PRELIMINARY NOTE. AS THE FIRST LOT OF GRANULATE PREPARED WITH* | | |
| | | *THIS BATCH SIZE AND PROCESS, THE WETTING PHASE WILL BE* | | |
| | | *PROCEEDED TO WITH EXTREME CAUTION.* | | |
| | | *A QUANTITY OF WATER EQUAL TO APPROXIMATELY HALF OF THE* | | |
| | | *THEORETICAL QUANTITY IS ADDED TO THAT OF POINT 6/1. THEN* | | |
| | | *APPROPRIATE PARTS ARE ADDED (6/2) UNTIL A GRANULATE IS OBTAINED* | | |
| | | *WHICH SATISFIES* [illegible]. | | |
| | | *THEORETICAL QUANTITY OF WATER = 277 IN WEIGHT => 4503 G x 27/100* | | |
| | | *=1216 g* | | |
| | | *QUANTITY TO WEIGH OUT AND ADD = 610 g* | | |
| | | [signature] | | |
| *10/04/01* | *3/2* | *ADD 600 g OF $H_20$ TO THE WET GRANULATE* | | |
| | | [signature] | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |



Checked by: [signature]

| | | | |
|---|---|---|---|
| Product: SU10398 | Lot: I83K01 | Room: | Attachment No.: *1* Page: *19* |
| Pharmaceutical form: Granulated | Dosage: 75% W/W in API | | |

| DATE | OPERATION No. | NOTES |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | [initials] *02/05/01* |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

| | |
|---|---|
| Operator's Signature: | Verifier's signature: |
| Edition No.: 7 of 10/05/99<br>Substitutes edition No.: 6 of 03/11/97 | Checked by: |

| Product: SU10398 | Lot: I83K01 | Page *20* of *20* |
|---|---|---|
| Pharmaceutical form: Granulated | Dosage: 75% W/W in API | |

## LOT APPROVAL

**OPERATIVE VERIFICATION of the "ORAL SOLIDS" SECTION**

**NOTES:** _____

SIGNATURE: [signature] DATE: *02/05/01*

**CHIEF of "ORAL SOLIDS and WAREHOUSING" APPROVAL**

RESULTS: APPROVED ☒ REJECTED ☐

**NOTES:** _____

SIGNATURE: [signature] DATE: *21/05/01*

**USE AUTHORIZATION OF THE CHIEF of "Q.C./PHARMACEUTICAL CONTROLS"**

RESULTS: APPROVED ☒ REJECTED ☐

**NOTES:** _____

SIGNATURE: [signature] DATE: *15/06/2001*

SF/ORAL SOLIDS

**PRODUCT** .....

**LOT** .....

**PREPARATION DATE** .....

**ATTACHED INDEXES**

| | | |
|---|---|---|
| 1. | ☐ | ACTIVE PRINCIPLE ANALYSIS REPORT |
| 2. | ☐ | IN PROCESS ANALYTIC CONTROLS REPORT |
| 3. | ☒ | PROCESS WATER REPORT |
| 4. | ☒ | ENVIRONMENTAL PARAMETER MONITORING |
| 5. | ☒ | RAW MATERIALS/PACKAGING MATERIALS REQUESTS |
| 6. | ☐ | FINISHED PRODUCT ANALYSIS REPORT |
| 7. | ☐ | BACTERIAL LOAD REPORT |
| 8. | ☒ | FINISHED PRODUCT DELIVERY FORM |
| 9. | ☐ | ANALYSES CERTIFICATE |
| 10. | ☐ | RAW DATA, in process weight controls. |
| 11. | ☒ | *SCHEDULED DEVIATION: WEIGH API IN ORAL SOLIDS PROCESSING ROOM* |
| 12. | ☒ | *SCHEDULED DEVIATION: INTERMEDIATE CLEANING ONLY BETWEEN LOTS SU 11248 AND SU10348* |
| 13. | ☐ | _____ |
| 14. | ☐ | _____ |

Note: _____

_____

Pharmacia&Upjohn

Pharmacia & Upjohn S.p.A.
Viale Pasteur, 10
20014 Nerviano (MI)
Italia

*LOT I83K01* [initials] *02 MAY 2001*
*ATTACHMENT 5*

**PHARMACEUTICAL DEVELOPMENT**

**ACTIVE PRINCIPLES REQUEST**

| PRODUCT | CODE | LOT |
|---|---|---|
| *SU10398* | *1502* | *(A) 5975-MTM-0002-N2* |

| QUANTITY REQUESTED IN GRAMS | SCALE | TITER |
|---|---|---|
| *3574.0* | * | |

| QUANTITY DELIVERED IN GRAMS | STORAGE |
|---|---|
| *3580* ** | *-20°C* |

| FINISHED PRODUCT LOT | PHARMACEUTICAL FORM | DOSAGE |
|---|---|---|
| *I83K01* | [initials] *03/04/01* ~~*CAPSULE*~~ *GRANULATE* | ~~*50g FREE BASE*~~ *75% W/W* [initials] *03/04/01* |

| TO BE MADE READY BEFORE | SCOPE OF THE REQUEST |
|---|---|
| *06/04/01* | *CLINICAL MANUFACTURING* |

| REQUESTING SECTION: | PRODUCT PREPARATION | PRODUCT COLLECTION |
|---|---|---|
| *ORAL SOLIDS* | | |
| Date: *03/04/01* | Date: *10-04-01* | Date: *10-04-01* |
| Signature: [signature] | Operator's signature: [signature] | Signature: [signature] |
| | Verifier's signature; [signature] | |
| | Chief's signature: [signature] | |

PROJECTS COORDINATION: _____

NOTE: * *Lot "under analyses"*

** [illegible] *done directly by the section* [signature] *10/4/01*

MTF017_5

**PHARMACEUTICAL DEVELOPMENT**

**EXCIPIENTS REQUEST**

| | | | | |
|---|---|---|---|---|
| PRODUCT: *SU10398* | | | | |
| LOT/PREPARATION: I83K01 | | | | |
| PHARMACEUTICAL FORM: [initials] *03/04/01* ~~*CAPSULE*~~ *GRANULATED* | | | DOSAGE: ~~*50 mg (as Free-base)*~~ *75% W/W* | |
| SCOPE OF THE PREPARATION: *CLINICAL MANUFACTURING* | | | | [initials] *03/0[4/01]* |
| EXCIPIENT NAME | CODE | LOT | QUANTITY (in grams) | UNDER ANALYSES |
| MANNITOL | *723* | *AE130* | *556.0* | |
| POLYVINYLPYRROLIDONE K25 | *931563000* | *AA10G041* | *233.3* | |
| CROSCARMELLOSE SODIUM | *920755200* | *AA10E113* | *140.0* | |
| CROSCARMELLOSE SODIUM | *920755200* | *AA10E113* | *140.0* | |
| VEGETABLE MAGNESIUM STEARATE | *927406000* | *AA10L028* | *23.3* | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| NOTES: *MAKE READY PRIOR TO 06/04/01* [initials] | | | | |

| REQUESTING SECTION: *ORAL SOLIDS* | PRODUCT PREPARATION | PRODUCT COLLECTION |
|---|---|---|
| Date: *03/04/01*<br>Signature: [signature] | Date: *04-04-01*<br>Operator's signature: [signature]<br>Verifier's signature: [signature]<br>Chief's signature: [signature] | Date: *10/04/01*<br>Signature: [signature] |

**PHARMACEUTICAL DEVELOPMENT**

**PACKAGING MATERIALS REQUEST**

| PACKAGING MATERIALS | | | | | |
|---|---|---|---|---|---|
| MATERIAL | CODE | LOT | QUANTITY REQUESTED | QUANTITY SENT | UNDER ANALYSES |
| *KRAFT BARRELS* | *771350000* | *VARIOUS* | *No. 2* | *2* | |
| *PE BAG FOR BARREL* | *735573000* | *AA39N054* | *No. 10* | *10* | |
| *PE BAG 350 X 580 mm* | *735190000* | *AA38L198* | *No. 10* | *10* | |
| *PE BAG 280 X 330 mm* | *735170000* | *AA38D091* | *No. 15* | *15* | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

| PRODUCT TO BE PACKAGED: | PHARMACEUTICAL FORM: |
|---|---|
| *SU10398* | *GRANULATE* |
| Dosage: *75% W/W IN API* | Lot: *I83K01* |

| REQUESTING SECTION *ORAL SOLIDS* | PRODUCT PREPARATION | PRODUCT COLLECTION |
|---|---|---|
| Date: *03/04/01* | Date: *05/04/04* | Date: *10/04/01* |
| Signature: [signature] | Operator's signature: [signature]<br>Verifier's signature: [signature]<br>Chief's signature: [signature] | Signature: [signature] |

*MTH014_4*

*NOTE. MAKE READY PRIOR TO 06 APRIL 2001* [initials]

*LOT I83K01* [initials] *02/05/01*

## PHARMACEUTICAL DEVELOPMENT / QUALITY ASSURANCE

## AUTHORIZATION TO USE THE PRODUCT WHILE IN THE UNDER ANALYSIS STATUS

---

---

The use of the product is authorized

Name/Initials *SU 10398*

Lot *(A) 5975-MTM-0002-N2*

Pharmaceutical form

Dosage

For *SU10398 – granulate lot I83K01 for clinic*

Date: **05 APR. 2001**

Signature [signature]

LOTTO I83K01
All. 4

eff 29/05/01

29-05-01 20:38 - 1- fabbC MAN-ORAL

RIEPILOGO ALLARMI SISTEMA C4

Point/Acknowledge Event Report with following specifications:

Start Date/Time : 10-04-01 08:00 Stop Date/Time : 11-04-01 17:00
Time Range : ---- days -- hours

Selected Events : Point Events

| | Point Keyname | Point Descriptor |
|---|---|---|
| 1 | 65C-33.0-CDZC4MIRIPMTH3 | UMID.RIPR.MOUNTER H3 LIMITE (25%RH |
| 2 | 65C-33.0-CDZC4MIRIPMTH4 | UMID.RIPR.MOUNTER H4 LIMITE (25%RH |
| 3 | 65C-33.0-CDZC4MIRIPMTH5 | UMID.RIPR.MOUNTER H5 LIMITE (25%RH |
| 4 | 65C-33.0-CDZC4MIRIPMTH6 | UMID.RIPR.MOUNTER H6 LIMITE (25%RH |
| 5 | 65C-33.0-CDZC4MIRIPMTH7 | UMID.RIPR.MOUNTER H7 LIMITE (25%RH |
| 6 | 65C-33.0-PILOCALE0025 | PRES.LOC.025 LIMITE (-0.8/0.0) |
| 7 | 65C-33.0-PILOCALE0026 | PRES.LOC.026 LIMITE (-0.8/0.0) |
| 8 | 65C-33.0-PILOCALE0029 | PRES.LOC.029 LIMITE (-0.8/0.0) |
| 9 | 65C-33.0-PILOCALE0030 | PRES.LOC.030 LIMITE (-0.8/0.0) |
| 10 | 65C-33.0-PILOCALE0033 | PRES.LOC.033 LIMITE (-0.8/0.0) |
| 11 | 65C-33.0-PILOCALE0034 | PRES.LOC.034 LIMITE (-0.8/0.0) |
| 12 | 65C-33.0-PILOCALE0037 | PRES.LOC.037 LIMITE (-0.8/0.0) |
| 13 | 65C-33.0-PILOCALE0038 | PRES.LOC.038 LIMITE (-0.8/0.0) |
| 14 | 65C-33.0-PILOCALE0043 | PRESSIONE LOCALE 043 LIMITE(-0.8/0.0) |
| 15 | 65C-33.0-PILOCALE0046 | PRESSIONE LOCALE 046 LIMITE(-0.8/0.0) |
| 16 | 65C-33.0-PILOCALE0053 | PRESSIONE LOCALE 053 LIMITE(-0.8/0.0) |
| 17 | 65C-33.0-PILOCALE0058 | PRES.LOC.058 LIMITE (-0.8/0.0) |
| 18 | 65C-33.0-PILOCALE0062 | PRES.LOC.062 LIMITE (-0.8/0.0) |
| 19 | 65C-33.0-PILOCALE0065 | PRES.LOC.065 LIMITE (-0.8/0.0) |
| 20 | 65C-33.0-PILOCALE0068 | PRES.LOC.068 LIMITE (-0.8/0.0) |
| 21 | 65C-33.0-PILOCALE0072 | PRES.LOC.072 LIMITE (-0.8/0.0) |
| 22 | 65C-33.0-PILOCALE0073 | PRES.LOC.073 LIMITE (-0.8/0.0) |
| 23 | 65C-33.0-PILOCALE0076 | PRES.LOC.076 LIMITE (-0.8/0.0) |
| 24 | 65C-33.0-PILOCALE0077 | PRES.LOC.077 LIMITE (-0.8/0.0) |
| 25 | 65C-33.0-PILOCALE0080 | PRES.LOC.080 LIMITE (-0.8/0.0) |
| 26 | 65C-33.0-PILOCALE0081 | PRES.LOC.081 LIMITE (-0.8/0.0) |

| LOG TIME | KEYNAME<br>SYSTEM ALARM TEXT<br>POINTDESCRIPTOR | VALUE<br>OPERATOR | ENG.UNIT<br>PREFIX |
|---|---|---|---|

*A total of 0 records were found for "Historical Activity Inquiry".*

END OF REPORT

[initials] *2/05/01*
*LOT I83K01 ATTACHMENT 8*

## Pharmacia & Upjohn

***PILOT PLANT FORMULATION DEVELOPMENT***

FINISHED PRODUCT DELIVERY FORM DATE: *11* / *04* / *2001*

PRODUCT: *SU10398* PREPARATION DATE: *04* / *01* APPROVED ☐

LOT: *I83K01* UNDER ANALYSES ☒

DOSAGE: *75% W/W* FORMULA NO.: */*

RAW MATERIAL LOT: *(A) 5975-MTM-0002-N2*

QUANTITY *4280* + COUNTER SAMPLE *1g* TOTAL *4281*

ADMINISTRATION: oral ☒ injectable ☐ topical ☐ drops ☐

PHARMACEUTICAL FORM

LYOPHILE ampoule ☐ vial ☐

SOLUTION/SUSPENSION bottle ☐ vial ☐ ampoule ☐ small flask ☐ bag ☐

OINTMENT tube ☐ jar ☐

gel ☐ cream ☐ paste ☐ salve ☐

TABLET simple ☐ film-coated ☐ sugar-coated ☐

gastrointestinal ☐ soluble/effervescent ☐

dimensions/form: _____

average weight: _____

packaging: _____

CAPSULE hard gelatin ☐ soft gelatin ☐

format: _____ average weight: _____

color: _____

printing: _____

packaging: _____

POWDER/GRANULATE oral ☒ injectable ☐ inhalational ☐

packaging: *Double P.E. bags/ Kraft Barrel*

STORAGE room temperature ☒ +4°C ☐ -20°C ☐ -80°C ☐

other conditions: _____

POSSIBLE NOTES: _____

PERSON IN CHARGE: [signature]

*LOT I83K01* [initials] *02/05/01*
*ATTACHMENT 3*

Pharmacia & Upjohn

## *Analyses Report*

*28-05-2001*



| | | | | | |
|---|---|---|---|---|---|
| ***Specifications:*** | V 0012PQ | Vers. 7 | ZZ DEMINERALIZED T.D.I. WATER | ***Lot:*** | CONTRAST 42 |
| ***Lot ID:*** | 700066554 | ***of*** 10 APRIL 2001 | ***Requester:*** 701 | ***Sample arrival:*** | 10 April 2001 |
| ***Request num.:*** | 200063176 | | | ***Planned finish:*** | 10 April 2001 |
| | | | | | 24 April 2001 |
| ***Product:*** | ZZ | | | ***Signatures of those in charge:*** | |
| ***Request Notes:*** | Collection on 10 April 2001 | | | | |
| | Requesting Section: Oral Solids | | | | CB GIANI 17 APRIL 2001 |
| | Contrast 42 used for the preparation of product SU10398 | | | | B GIANI 17 APRIL 2001 |
| | Lot: I83K01 | | | **Analyses finish** | CRISTINA 18 APRIL 2001 |

***Characteristics:*** Clean colorless liquid

***Storage method:***

| *Phase* | *Method* | *Vs.* | *Description* | *M.U.* | (----------Limits----------) (-Min-) | (-Max-) | (----Test----) | Result | Quantity | Page | Signed |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 9706xx | 4 | TOTAL AEROBIC MICROORGANISMS | UFC/ml | 50 | | 0 | | 2505 | 8 | GALIMLAO |

*LOT I83K01* [initials] *28 MAY 2001*
*ATTACHMENT 11*

# SCHEDULED DEVIATION REQUEST

| SECTION: | No.: |
|---|---|
| Warehouse | *13/01* (as performed by the QA/Quality Systems Section) |

DOCUMENT NUMBER AND TITLE:

SOP SF.TD 077
SOP SF.TH 017

| PRODUCT/MATERIAL/LOT: | ACTIVITY: |
|---|---|
| SU-10398 API<br>Lot: (A) 5975-MTM-0002-N2 | Product requested for the preparation of granulate (lot: I83K01) intended for preparations for clinical use. |

DESCRIPTION OF PROPOSED DEVIATION:

Performed the weighing in room 072 of the Orals Solid Products R&D section rather than in the laminar flow cabin (machine ID: MGZ/FL/002) positioned in room 909, as provided for in the procedure.
The weighing operations performed by Oral Solid Products R&D personnel.

MOTIVATION:

Due to the particular nature of the product (excessively coloring) it was desired to avoid rendering the laminar flow cabin unusable for several days (with the consequential delays in the fractioning/sampling operations), for the time needed to carry out an accurate cleaning of the cabin.

SIGNATURE/DATE [signature] N. Gabriele Apr. 03, 2001

For a process, provide the start and end dates of the process in advance:

April 09, 2001 - *April 30, 2001* [signature] *05/04/01*

**DEVIATION APPROVAL**

| SECTION CHIEF: | QA/QUALITY SYSTEMS: |
|---|---|
| [signature] | [signature] *05.04.2001* |

**Attachment to the SCHEDULED DEVIATION REQUEST No. *13/01***

INTERVENTIONS TO BE PERFORMED

In order to guarantee the safety of the operators individual protection systems must be adopted for the work in question.

Furthermore in order to guarantee the appropriate operations documentation and traceability of the product movements the interventions below listed must be carried out:

1. All the weighing operations and their relative recording must be performed by an operator in the presence of a verifier, each of whom at the end of the operations will sign and date the relative documentation.
2. Verify that room 072 is clean and clear of the materials used for the previous process.
3. Verify that the scale to be used is properly approved, calibrated, and verified with the sample weight and is zeroed.
4. Perform the weighing of the active principle, recording all the operations performed in the section pertinent to the Batch Record.
5. Fill in the Active Principles Request Form, and indicate the quantity of active principle weighted out, then sign and date as indicated in 1.
6. Close the container containing the active principle and clean the outside of it with rags wet with water.
7. Close the room's container prior to beginning the processing.
8. Deliver the active principle container to the Warehouse, along with the documentation stating the amount removed.
9. Proceed to the registration of the material transactions.

Quality Assurance/Quality Systems [signature] *05.04.2001*

[Lot 183] *K01* [initials] *29/05/01*
*ATTACHMENT 12*

# SCHEDULED DEVIATION REQUEST

| **SECTION: Oral Solid Products R&D** | **No.:** *14/01* (as performed by the QA/Quality Systems Section) |
|---|---|

DOCUMENT NUMBER AND TITLE:
SF.TD 069 Vers. 2: Cleaning of the equipment for the preparation of oral solids pharmaceutical products.

| PRODUCT/MATERIAL/LOT: | ACTIVITY: |
|---|---|
| SU010398 Lot (A) 5975-MTM-0002<br>(malate salt of SU011248) | Production of granulated lot 183K01<br>Production of capsules lot 183G02 |

DESCRIPTION OF PROPOSED DEVIATION:
Execution of intermediary cleaning of the equipment previously used for the processing of SU011248 (lots 182K01 and 182G02).
The cleaning of the equipment by vacuum and the cleaning of the fluid bed granulator is to be carried out with TDI Water. Then we will proceed to sampling the equipment used in the points indicated in the communication of 2 April (see Attachment 1) solely for informative purposes.

MOTIVATION:
The technical rationale for the deviation is provided in the attached documentation:
Attachment 2: Memorandum by Sardar Ali (09/02/01)
Attachment 3: Communication by David Hahn (14/02/01)

SIGNATURE/DATE [signature] *06/04/01*

For a process, provide the start and end dates of the process in advance:

~~17-20 April 2001~~ *09-30 April 2001* [signature] *06/04/01*

**DEVIATION APPROVAL**

| **SECTION CHIEF:** | **QA/QUALITY SYSTEMS:** |
|---|---|
| [signature] | [signature] *April 6th, 2001* |

Author: Paolo Gatti at itnerpo4
Date: 4/2/01 4:55 PM
Priority: Normal
CC: Rosaria Mariani, Luciano Gambini, Paolo DellaVedova, Mauro Ulivieri, Donata Giudici at ITNERPO1
TO: Irma Facchetti

[Subject:] Re [3]: Intermediate cleaning between the manufacturing of SU011248 and SU010 capsules.

Hi Everyone,

Luciano and I have defined which points to sample and analyze in the machines used for the processing of SU11248 cleaned with intermediate cleaning prior to working on SU10398.

It has been decided that one point per machine will be sampled, considering that the result with the greatest residue per unit is superficial after the greater cleaning performed prior to the first lot of SU11248 capsules.

In absolute, the following points will be sampled and analyzed (here is the detailed list for Giorgio who will prepare the swabs accordingly):

| | | |
|---|---|---|
| Zanasi capsule sealer | Hopper base | (OP/05/1P) |
| Viani Oscillating Granulator | Rear rotor housing | (GS/03/1P) |
| Glatt 5 Fluid bed dryer | Spy zone | (LF/02/1P) |
| Diosna Speed Granulator | Crusher | |
| Pellegrini V Mixer | Bottom | (MS/27/2P) |

I spoke with Giorgio and tomorrow he will take the samples and send the swabs to Rita.

The list of sample points will be inserted into the scheduled deviation that will be drawn up to support the "in campaign" processing of the two products which have different instructions (11248 and 10398).
I will meet tomorrow morning with Luciano and Donata about this.

Bye everyone.

Paolo

_____ Reply Separator _____
Subject: Re[2]: Cleaning intermedio fra mfg capsule SU011248 ed SU010
Author: Irma Facchetti at itnerpo4
Date: 02/04/01 14.21

Paolo,
I'm sorry for the lack of understanding about the deviation.

When operation methods different from those described in a SOP are adopted (such as in this case), it is necessary to follow the procedure regarding the deviations.

Bye,
Irma

_____ Reply Separator _____
Subject: Re: Cleaning intermedio fra mfg capsule SU011248 ed SU010398
Author: Paolo Gatti at itnerpo4
Date: 4/2/01 1:09 PM

Irma,
With regard to the scheduled deviation, I would ask that you forward Sugen's memo and Dave's email to me so that I can get things going as soon as possible with Donata. Only one thing is not clear. It is the first time I have heard about the need for scheduled deviation even though it's been at least a month that we've known we would have only done one intermediate cleaning. I have nothing against doing these documents, and I'm absolutely not arguing, but sometimes it would be better if things were defined a little bit in advance.

In my opinion, the same is true for the sampling and analyses. Tomorrow Giorgio will sample the machines in all the points indicated

by the respective cleaning SOP (I think we all agree on this), so that the analyses can be performed. However the execution time is also linked to the availability of Rita's group, as well as to the decision regarding which points are effectively to be analyzed.
I repeat my warning (and I think Rita would agree...) that it is not logical to analyze all the points if they are not strictly necessary according to the rationale with which this verification is to be handled, and which I will evaluate first with Paolo DellaVedova to be sure I have properly understood.

Thank you for your quick update after our chat this morning.

Bye,
Paolo

_____ Reply Separator _____
Subject: Cleaning intermedio fra mfg capsule SU011248 ed SU010398
Author: Irma Facchetti at itnerpo4
Date: 02/04/01 12.49

Paolo,

Speaking as QA, I ask that you:

-open a scheduled deviation request and attach the documents detailing the rationale. There is a Memo by Sugen and an E-mail by Dave which will be formalized into a Memo shortly.

With regard to the sampling requested by Shahe:

-within the bounds of the cleaning procedure, for an intermediate type cleaning, no sampling is provided for. The choice of critical points to be examined will be defined with Paolo Della Vedova.

-it would be advisable to carry out these doses within the shortest possible time provided that there is no data or valid rationale which would allow claims to be made regarding the stability of the product under the conservation conditions and time periods that are to be defined.

Best regards
Irma

SUGEN

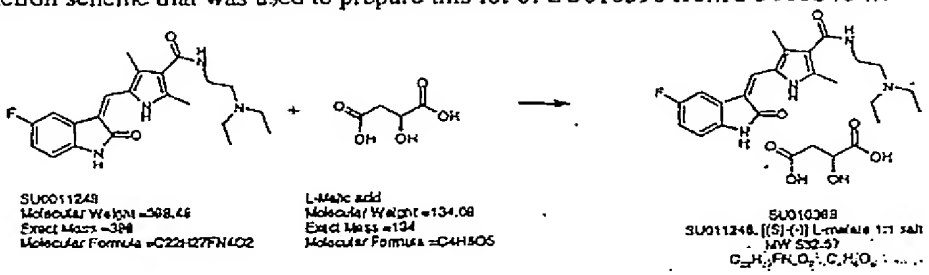
**Memorandum**

| | | | |
|---|---|---|---|
| To: | Sardar Ali | From: | Peter Giannousis |
| Dept: | | Dept: | PCPD – Analy & Chem. Dev. |
| Loc./Tel. | | Loc./Tel. | B2-2403 : X3705 |
| Cc: | Arun Koparkar, James Gage, Bhavesh Patel | Date: | 09-Feb-01 |
| Subject: | Genealogy of SU010398 lot (A)5975-MTM-0002 | | |

Dear Sardar,

Per your request, the following is a summary of the genealogy of SU010398 lot (A)5975-MTM-0002.

The reaction scheme that was used to prepare this lot of SU010398 from SU011248 is:




**In fact SU011248 lot (A2)5953-TJF-0003 was used as starting material to prepare SU010398 lot (A)5975-MTM-0002.** SU010398 is the L-malate salt of SU011248, and as such contains about 75% of SU011248 by weight.

The impurities in SU011248 lot (A2)5953-TJF-0003 were higher than those in the previous lots of SU011248 that were tested in GLP toxicological studies. Therefore SU011248 lot (A2)5953-TJF-0003 was qualified for human use by repeating the 2-week tox study. A memo was issued in early January from Toxicology, certifying that there were no significant differences seen in the tox studies with the new lot versus previous lots of SU011248.

**The impurities in SU010398 lot (A)5975-MTM-0002 were found to be similar or lower than those in SU011248 lot (A2)5953-TJF-0003.** In fact this lot of SU010398 is being used in 3-month GLP tox studies, with results available in May-June 2001.

Based on these facts, it would be expected that there should be no contamination issues in sequential capsule manufacture, as long as the bulk of the SU011248 and the excipients are removed from the equipment. In other words, one would expect that the API impurities would be comparable, and the amount of freebase left in the equipment should be much less than weighing errors of the L-malate salt.

Peter Giannousis

Author: David A Hahn at ITNERPO5
Date: 2/14/01 4:39 PM
Normal
TO: bhavesh-patel@sugen.com at SUGEN, chandu-hegde@sugen.com at SUGEN, peter-giannousis@sugen.com at SUGEN, sardar-ali@sugen.com at SUGEN
CC: Marco Adami at ITNERPO4, Marina Baldi at ITNERPO4, Irma Facchetti at ITNERPO4, Paolo Gatti at ITNERPO4, Rosaria Mariani at ITNERPO4, Mauro Ulivieri at ITNERPO4, Luciano Gambini at ITNERPO4
Subject: Re: Sequential capsule manufacturing from free base and L-ma
---------- Message Contents

Sardar,

Here is the general logic that I have in mind. This could be developed in more depth, or in a different way (to the extent allowed by the data). Please let me know what you think.

(1) Solubility and rotating disk dissolution rate data indicate that both the free base and the malate salt have solubility "more than sufficient to prevent solubility from being a limiting factor in the bioavailability," according to Study Report a0089789. Thus, a small amount of one material in the other would not be expected to have any impact on biological performance.

(2) Paolo estimates that after the proposed dry cleaning that the amount of granulation remaining would certainly be less than 10 grams (probably much less). If as much as 10 g remained, this would amount to less than 0.2% of a 5.3 kg granulation batch (using 3.5 kg FBE of API). Given the similar dissolution behaviors, the presence of 0.2% of a granulation of one salt in a granulation of the other would not be expected to influence the biological performance.

(3) Because the process uses wet granulation, the granulated material of which traces would remain on the surfaces of the equipment would likely be representative of the previous granulation, and would likely be incorporated homogeneously into the subsequent granulation. Thus, the presence of a small amount of material from the previous granulation would not be expected to significantly alter the chemical or physical properties of the subsequent granulation.

(4) And I understand that Peter is developing a rationale for safety of the impurity levels based on the geneological relationship between the batches involved and based on the fact that the qualified impurities levels would allow use of either batch in humans.

Please let me know if you have any comments, questions or concerns.

Ciao,

Dave

---------- Reply Separator ----------
Subject: Sequential capsule manufacturing from free base and L-malate
Author: Sardar Ali <sardar-ali@sugen.com> at SMTP-KZO
Date: 2/12/01 5:37 PM

Dear Dr. Hahn,

ing in Nerviano (during my visit) with Irma, and Rita discussed the impact of sequential capsule manufacturing from free base and L-malate salt API's. As we discussed that the equipment will be dry cleaned (removing excipients from the equipment) after completing one batch and before moving to the next batch with different excipient.. What we agreed was to get some scientific rationale from you and Peter to assure that the amount of free base traces left in the equipment will be non-detectable. . Peter is preparing a summary of genealogy of SU010398 lot (A)5975-MTM-002 to justify that impurities in SU010398 are similar or lower than those in SU011248 lot. I will appreciate if we get some scientific rationale from you regarding this what you had agreed to provide us.

I am sorry that I did not get back to you earlier because the manufacturing plan was changed when I returned (Capsule manufacturing from the free base API only) but now it has been changed back to the same what we had discussed.

With Best Regards

Sardar Ali
QA Product Release Manager
SUGEN, Inc.
230 East Grand Avenue
South San Francisco
Phone: (650) 837-3648
Fax: (650) 837-3326